

WHAT IS CLAIMED IS:

1. A fusion protein having binding specificity for human interleukin-4 (IL4) which comprises complementarity determining regions (CDRs) derived from a non-human neutralizing monoclonal antibody characterized by a dissociation constant equal to or less than 2×10^{-10} M for human IL4, and a first fusion partner.
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2. The fusion protein according to claim 1 which is operatively linked to a second fusion partner.
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3. The fusion protein according to claim 1 wherein said non-human neutralizing monoclonal antibody is selected from the group consisting of 3B9 and 6A1.
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4. The fusion protein according to claim 2 wherein said second fusion partner comprises all or part of an immunoglobulin constant heavy chain or immunoglobulin constant light chain, or both.
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5. The fusion protein according to claim 1 wherein said first fusion partner sequence is the heavy chain sequence of: amino acids 21-50, 56-71, 88-119, and 131-141 of SEQ ID NO:12.
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6. The fusion protein according to claim 1 wherein said first fusion partner sequence is the light chain sequence of: amino acids 20-42, 58-72, 80-111, and 121-131 of SEQ ID NO: 14.
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7. The fusion protein according to claim 1 wherein said amino acid sequences of the complementarity determining regions for the heavy chain are:
 - (a) ThrSerGlyMetGlyValSer: SEQ ID NO:22,
 - (b) HisIleTyrTrpAspAspAspLysArgTyrAsnPro-SerLeuLysSer: SEQ ID NO:24, or
 - (c) ArgGluThrValPheTyrTrpPheAspVal: SEQ ID NO:26.
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8. The fusion protein according to claim 1 wherein said amino acid sequences of the complementarity determining regions for the light chain are:
 - (a) LeuAlaSerGlnSerValAspTyrAspGlyAspSerTyrMetAsn: SEQ ID NO:16,

- (b) AlaAlaSerAsnLeuGluSer: SEQ ID NO:18, or
- (c) GlnGlnSerAsnGluAspProProArg: SEQ ID NO:28.

9. The fusion protein according to claim 1 wherein said amino acid sequences of the complementarity determining regions for the light chain are:

- (a) LysAlaSerGlnSerValAspTyrAspGlyAspSerTyrMetAsn: SEQ ID NO:16,
- (b) AlaAlaSerAsnLeuGluSer: SEQ ID NO:18, or
- (c) GlnGlnSerAsnGluAspProProThr: SEQ ID NO:20.

10. 10. An immunoglobulin heavy chain complementarity determining region (CDR), the amino acid sequence of which is selected from the group consisting of:

- (a) ThrSerGlyMetGlyValSer: SEQ ID NO:22,
- (b) HisIleTyrTrpAspAspAspLysArgTyrAsnPro-SerLeuLysSer: SEQ ID NO:24, and
- (c) ArgGluThrValPheTyrTrpPheAspVal: SEQ ID NO:26.

11. 20. An immunoglobulin light chain complementarity determining region (CDR), the amino acid sequence of which is selected from the group consisting of:

- (a) LeuAlaSerGlnSerValAspTyrAspGlyAspSerTyrMetAsn: SEQ ID NO:16,
- (b) AlaAlaSerAsnLeuGluSer: SEQ ID NO:18,
- (c) GlnGlnSerAsnGluAspProProArg: SEQ ID NO:28; and
- (d) GlnGlnSerAsnGluAspProProThr: SEQ ID NO:20.

12. 30. A nucleic acid molecule encoding an immunoglobulin heavy chain complementarity determining region (CDR), the sequence of which is selected from the group consisting of:

- (a) ACT TCT GGT ATG GGT GTG AGC: SEQ ID NO:21,
- (b) CAC ATT TAC TGG GAT GAT GAC AAG CGC TAT AACCCATCCCTGAAGAGC: SEQ ID NO:23,
- (c) AGA GAG ACT GTG TTC TAC TGG TAC TTC GAT GTC: SEQ ID NO:25,
- (d) ACC TCC GGT ATG GGT GTT TCC: SEQ ID NO: 54,
- (e) CAC ATC TAC TGG GAC GAC GAC AAA CGT TAC AAC CCG AGC CTG AAA TCC: SEQ ID NO: 55, and

(f) CGC GAA ACC GTT TTC TAC TGG TAC TTC GAC GTT: SEQ
ID NO: 56.

13. A nucleic acid molecule encoding an immunoglobulin light chain
5 complementarity determining region (CDR), the sequence of which is selected from
the group consisting of:

(a) AAG GCC AGC CAA AGT GTT GAT TAT GAT GGT
GAT AGT TAT ATG AAC: SEQ ID NO:15,
(b) AAG GCC TCC CAA AGT GTT GAT TAT GAT GGT GAT AGT
10 TAT ATG AAC: SEQ ID NO: 53,
(c) GCT GCA TCC AAT CTA GAA TCT: SEQ ID NO:17, (d)
CAG CAA AGT AAT GAG GAT CCT CCG ACG: SEQ ID NO:19, and
(e) CAG CAA AGT AAT GAG GAT CCT CCG-AGG: SEQ ID NO:27.

15 14. A humanized antibody comprising a heavy chain and a light chain,
said antibody characterized by a dissociation constant equal to or less than about 2×10^{-10} M for human IL4, wherein the framework regions of said heavy and light
chains are derived from at least one selected human antibody and the amino acid
sequences of the complementarity determining regions of each said chain are
20 derived from a non-human neutralizing monoclonal antibody specific for human IL4
characterized by a dissociation constant equal to or less than about 2×10^{-10} M for
human IL4.

15. The antibody according to claim 14 wherein said antibody is
25 optionally linked to an effector agent selected from the group consisting of a non-
protein carrier molecule, polystyrene, and plastic beads.

16. A chimeric antibody comprising a heavy chain and a light chain, said
antibody characterized by a dissociation constant equal to or less than about 2×10^{-10} M for human IL4, wherein the amino acid sequences of the complementarity
30 determining regions of said heavy chain and said light chain are derived from a non-
human neutralizing monoclonal antibody specific for human IL4 characterized by a
dissociation constant equal to or less than about 2×10^{-10} M for human IL4.

35 17. A pharmaceutical composition comprising the fusion protein of claim
1 and a pharmaceutically acceptable carrier.

18. A method of treating allergies and other conditions associated with excess IgE production in a human comprising the step of administering to said human in need thereof an effective amount of the fusion protein of claim 1.

5 19. An isolated nucleic acid sequence which is selected from the group consisting of:

- (a) a nucleic acid sequence encoding the fusion protein of claim 1;
- (b) a nucleic acid sequence complementary to (a);
- (c) a nucleic acid sequence of 18 or more nucleotides capable of hybridizing to (a) or (b) under stringent conditions; and
- (d) a fragment or analog of (a), (b), or (c) which encodes a protein characterized by having specificity for human interleukin-4; wherein said sequence optionally contains a restriction site.

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20. The isolated nucleic acid sequence according to claim 19, wherein the sequence encoding the fusion protein comprises the nucleic acid sequence of Fig. 5, SEQ ID NO:13.

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21. The isolated nucleic acid sequence according to claim 19, wherein the sequence encoding the fusion protein comprises the nucleic acid sequence of Fig. 4, SEQ ID NO:11.

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22. An isolated nucleic acid sequence which is selected from the group consisting of:

- (a) a nucleic acid sequence encoding a complementarity determining region (CDR) wherein said CDR is obtained from a neutralizing murine monoclonal antibody specific for human interleukin-4 and having a dissociation constant equal to or less than about 2×10^{-10} M;
- (b) a nucleic acid sequence complementary to (a);
- (c) a nucleic acid sequence of 18 or more nucleotides capable of hybridizing under stringent conditions to (a) or (b); and
- (d) a fragment or analog of (a), (b) or (c) which encodes a protein characterized by having specificity for human interleukin-4.

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23. The isolated nucleic acid sequence according to claim 22, wherein said sequence is selected from the group of heavy chain complementarity determining region-encoding sequences consisting of:

- (a) ACT TCT GGT ATG GGT GTG AGC: SEQ ID NO:21,
- 5 (b) CAC ATT TAC TGG GAT GAT GAC AAG CGC TAT AAC CCA TCC CTG AAG AGC: SEQ ID NO:23,
- (c) AGA GAG ACT GTG TTC TAC TGG TAC TTC GAT GTC: SEQ ID NO:25,
- (d) ACC TCC GGT ATG GGT GTT TCC: SEQ ID NO: 54,
- 10 (e) CAC ATC TAC TGG GAC GAC GAC AAA CGT TAC AAC CCG AGC CTG AAA TCC: SEQ ID NO: 55, and
- (f) CGC GAA ACC GTT TTC TAC TGG TAC TTC GAC GTT: SEQ ID NO: 56.

15 24. The isolated nucleic acid sequence according to claim 22, wherein said sequence is selected from the group of light chain complementarity determining region-encoding sequences consisting of:

- (a) AAG GCC AGC CAA AGT GTT GAT TAT GAT GGT GAT AGT TAT ATG AAC: SEQ ID NO:15,
- 20 (b) AAG GCC TCC CAA AGT GTT GAT TAT GAT GGT GAT AGT TAT ATG AAC: SEQ ID NO: 53,
- (c) GCT GCA TCC AAT CTA GAA TCT: SEQ ID NO:17, (d) CAG CAA AGT AAT GAG GAT CCT CCG ACG: SEQ ID NO:19, and
- (e) CAG CAA AGT AAT GAG GAT CCT CCG AGG: SEQ ID NO:27.

25 25. A recombinant plasmid comprising the nucleic acid sequence of claim 19.

30 26. A recombinant plasmid comprising the nucleic acid sequence of claim 22.

27. A host cell transfected with the recombinant plasmid of claim 25.

35 28. A host cell transfected with the recombinant plasmid of claim 26.

29. A process for producing a humanized antibody specific for human interleukin-4 comprising culturing a cell line transfected with the recombinant

plasmid of claim 25 under the control of selected regulatory sequences capable of directing the expression thereof in said cells.

30. A method for diagnosing allergies and other conditions associated
5 with excess immunoglobulin E production in a human which comprises contacting a sample of biological fluid with a high titer monoclonal antibody for human IL4 and assaying for the occurrence of binding between said monoclonal antibody and human interleukin 4.

10 31. A method for screening monoclonal antibodies which have a high titer for human interleukin 4 which comprises:
a) preparing a hybridoma cell line characterized by secretion of a monoclonal antibody to human interleukin 4; and
b) screening said hybridoma cell line with aldehyde-coupled
15 human interleukin-4 or biotinylated human interleukin-4.

32. A neutralizing monoclonal antibody having a high titer for human interleukin-4, a Fab fragment or a $F(ab')_2$ fragment thereof, produced by screening a library of hybridoma products with aldehyde-coupled human interleukin-4 or
20 biotinylated human interleukin-4.

33. A rodent neutralizing monoclonal antibody specific for human interleukin-4 and having a binding affinity characterized by a dissociation constant equal to or less than about 2×10^{-10} M.
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34. The monoclonal antibody according to claim 33 wherein said rodent is a mouse.

35. The monoclonal antibody according to claim 34, which comprises the light chain amino acid sequence of SEQ ID NO: 2, and the heavy chain amino acid sequence of SEQ ID NO: 4.
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36. The monoclonal antibody according to claim 33, wherein said rodent is a rat.
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37. The monoclonal antibody according to claim 36 having the identifying characteristics of 6A1.

38. A hybridoma having the identifying characteristics of cell line
3426A11C1B9.